# International, multicentre Naturalistic Cohort study of Attention Deficit/Hyperactivity Disorders (ADHD) and Substance use disorders (SUD): clinical characteristics, treatment and outcome at 1-, 3- and 9-months follow-up (INCAS)

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## 1. BACKGROUND

Childhood attention deficit hyperactive disorder (ADHD), which involves inattention, hyperactivity and impulsivity, and its persistence into adulthood, is associated with a high risk of the development of substance use disorders (SUDs) (1-3). Adult ADHD is highly prevalent in treatment seeking SUD patients. The International ADHD in SUD Prevalence Study (IASP) recently found an ADHD prevalence of 16 % in adult treatment seeking substance users. In a recent meta-analysis, 23% of all treatment seeking SUD patients met diagnostic criteria for adult ADHD (4).

However, there is a lack of knowledge regarding the efficacy of treatments for combined ADHD and SUD. A series of randomized controlled trials with a standard dose of the psychostimulant methylphenidate, one of the most commonly used medications for adult ADHD, failed to show any significant main effects on the primary outcome variables selected, such as reduction of ADHD symptoms or reduction of alcohol or drug use (5). However, one randomized placebo-controlled study using atomoxetine for the treatment of patients with alcohol dependence and ADHD demonstrated encouraging results, with reductions in both ADHD symptoms and alcohol consumption (6). A more recent randomized placebo-controlled study using methylphenidate doses up to 180 mg/day showed significant reductions in both ADHD symptoms and drug consumption in amphetamine dependent criminal offenders with ADHD (7). The most recent study tested the effect of extended-release mixed amphetamine salts using to doses in robust doses (60 and 80 mg) along with cognitive behavioural therapy (CBT) and found improvements in both ADHD symptoms and drug use in patients with cocaine dependence and comorbid ADHD (8). Finally, an on-going study is testing the effectiveness of integrated CBT for SUD patients with adult ADHD (9).

Whereas these clinical trials typically address the efficacy of a specified intervention in a selected population, they provide very limited knowledge on the natural course of the disorders and on predictors of treatment effectiveness in routine clinical settings of SUD treatment.

The rationale of this research project, a naturalistic observational study, is to describe the different treatment modalities provided in the SUD health care systems of various European countries and the USA and to assess relevant outcomes regarding ADHD symptoms and substance use in adult treatment seeking SUD patients with an ADHD. We will estimate the effectiveness of different treatment modalities, we will identify potential predictors of and their relationship to the treatment effectiveness, and we will examine safety profiles of the pharmacological treatments.

## 2. OBJECTIVES, ENPOINTS/OUTCOMES AND OTHER STUDY VARIABLES

### 2.1 Objectives

Five objectives are pursued:
(1) To describe the treatments modalities provided to treatment seeking SUD patients with comorbid adult ADHD;
(2) To describe differences in outcome for different treatment modalities (pharmacological psychological/psychosocial treatment),
(3) To identify predictors (such as gender, SUD and ADHD severity, comorbidity) for retention in treatment, ADHD symptoms, and substance use;
(4) To investigate the safety profile of pharmacological treatment of ADHD in a naturalistic cohort of treatment seeking substance users with regard to adverse events (e.g. cardiovascular, psychiatric, misuse and diversion of medication); and
(5) To derive hypotheses for future randomized trials.

### 2.2 Primary and secondary endpoint/outcome(s)

Primary outcomes are ADHD symptoms and substance use at admission, 1-, 3, and 9-month follow-up.

Secondary outcomes are retention to the treatment, and at 3- and 9-month follow-ups the employment, use of emergency services, number of accidents, and safety profile of pharmacological treatment of ADHD.

### 2.3 Other study variables

A number of potential predictors of the outcomes at 1-, 3- and 9-month follow-up will be of key interest. These are the following baseline variables: age, gender, employment status; social status; substances used, including nicotine; frequency of use; route of administration, that is oral, nasal, inhalant, dermal, rectal, or injection; ADHD severity; current psychiatric diagnoses; self-efficacy related to substance use; anger and aggression; sensitivity to punishment and reward; difficulties in emotional regulation; religious salience; and quality of life.

## 3. PROJECT DESIGN

This is an international, naturalistic, multicenter, observational cohort study with an overall sample of 600 treatment seeking adult SUD patients with adult ADHD. In Switzerland, data of up to 100 patients from 10 treatment centers in canton Berne, Aargau and Zurich will be collected at baseline (treatment initiation), at 1 month, at three months, and at nine months after inclusion to assess the course of ADHD symptoms and substance use. These two dependent main variables will be correlated with the independent variable, that is ADHD treatment modalities (i.e., stimulants such as short or long-acting methylphenidate, (lis-) dexamphetamine, racemic amphetamine salts atomoxetine, neurofeedback, ADHD-specific psychological treatment or combinations of them) and no ADHD-specific treatment to investigate differential courses of the two main variables depending on the various treatment modalities.

The external validity of the naturalistic observational study is high revealing treatment practices of ADHD in SUD treatments, the primary aim of this project, but the internal validity is low so that only correlational but no causal relationship can be described. The main problem is that a large sample is needed to find statistically significant patterns between differential courses and treatment modalities. Therefore nine European countries including Switzerland and the USA will participate in the study to obtain 600 SUD treatment seeking patients with both ADHD and SUD.

## 4. PROJECT POPULATION

### 4.1 Inclusion criteria

Male and female patients of ≥18 and ≤65 years of age who are seeking treatment for SUD at any of the participating sites having a

- clinical ADHD diagnosis according to DSM-IV/DSM-5 (11, 12)
- clinical SUD diagnosis (DSM-5 moderate to severe, ICD-10 dependence) (13)
- signed informed consent

### 4.2 Exclusion criteria

There are no formal exclusion criteria except those patients that are not able or not willing to complete the assessments.

## 5. REFERENCES


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